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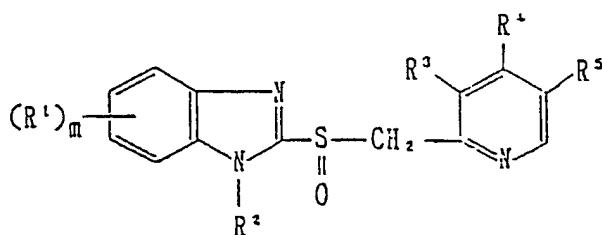
(71) Applicant: Takeda Chemical Industries, Ltd.
27, Doshomachi 2-chome Higashi-ku
Osaka-shi Osaka, 541(JP)

(72) Inventor: Makino, Tadashi
39-1 12 Mishimaoka 2-chome
Ibaraki Osaka 567(JP)
Inventor: Tabata, Tetsuro
C-407, 52 Yamadanishi 3-chome
Suita Osaka 565(JP)
Inventor: Hirai, Shin-ichiro
201, Tamamoto-cho
Aburakojidori-shomensagaru
Shimogyo-ku Kyoto 600(JP)

(74) Representative: Laredo, Jack Joseph et al
Elkington and Fife High Holborn House 52/54
High Holborn
London, WC1V 6SH(GB)

(54) Stabilized pharmaceutical composition comprising a benzimidazole compound, its production and its use as an antiulcer agent.

(57) The pharmaceutical composition of the invention, which comprises a benzimidazole compound of the formula



wherein R¹ is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R² is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl, R³ and R⁵ are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R⁴ is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4, and a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium, is physically stable.

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Stabilized Pharmaceutical Composition and Its Production

This invention relates to a pharmaceutical composition which comprises 2-[(2-pyridyl)methylsulfinyl]benzimidazole or a derivative thereof (hereinafter sometimes referred to collectively as "benzimidazole compounds"), which is useful as an antiulcer agent, as stabilized by incorporation of a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium and its production.

5 Certain benzimidazole compounds have recently been under clinical study as gastric acid secretion inhibitors. They serve as therapeutic agents for digestive ulcers. Their principal pharmacological effect consists in gastric acid secretion suppression based on ($H^+ + K^+$)-ATPase inhibition and is more potent and durable as compared with histamine H₂ receptor antagonists such as cimetidine and ranitidine. They also have gastric mucosa protecting activity. Therefore, they have attracted attention as next-generation
10 potent therapeutic agents for digestive ulcers.

Those benzimidazole compounds which are described in Japanese Unexamined Patent laid open Nos. 62275/77, 141783/79, 53406/82, 135881/83, 192880/83 and 181277/84, corresponding to U.S. Patent No. 4,045,563, U.S. Patent No. 4,255,431, European Patent Publication No. 45,200, U.S. Patent No. No. 4,472,409, European Patent Publication No. 5,129 and G.B. Patent Publication No. 2,134,523A, respectively,
15 among others are known to have antiulcer activity.

These compounds, however, have poor stability. In the solid state, they are susceptible to heat, moisture and light and, in aqueous solution or suspension, their stability decreases with decreasing pH. In dosage forms, i.e. tablets, powders, fine granules, granules and capsules, said compounds are apt to interact with other components contained in said dosage forms and accordingly are in a less stable state as
20 compared with the case where they occur alone. Thus, the content decreases and the color changes significantly in the manufacturing process of dosage form and with the lapse of time. Microcrystalline cellulose, polyvinylpyrrolidone (PVP), carboxymethylcellulose calcium, polyethylene glycol 6000 and Pluronic F68 (polyoxyethylene-polyoxypropylene copolymer), for instance are dosage form components adversely affecting the stability of said compounds. Furthermore, in the case of coated tablets and coated
25 granules among the above dosage forms, enteric coating bases such as cellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate and Eudragit (methacrylic acid-acrylic acid copolymer) have poor compatibility with said compounds and cause content decrease and color change. Nevertheless, one or more of these components or ingredients, which, as mentioned above, can produce adverse effects
30 on the stability of said compounds, are essential in the manufacture of oral preparations and therefore difficulties are inevitably encountered in dosage form manufacture.

The prior art avoids the above-mentioned stability problem by using said benzimidazole compounds in a salt form, say in the form of a lithium, sodium, potassium, magnesium, calcium or titanium salt [Japanese Unexamined Patent laid open No. 167587/84 (European Patent Publication No. 124,495A)]

However, the above prior art method requires, for the stabilization of the benzimidazole compounds, a
35 step of converting said compounds to such a salt form as mentioned above in advance.

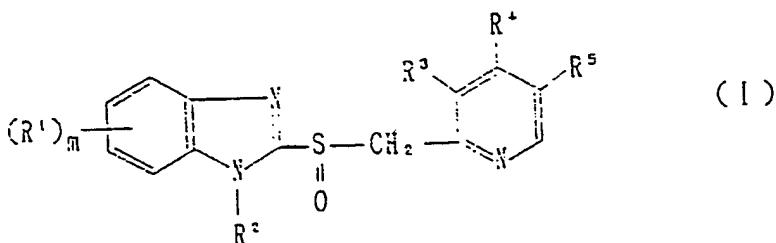
In view of the above, the present inventors made investigations in an attempt to stabilize pharmaceutical preparations containing benzimidazole compounds and, as a result, have completed the present invention.

Thus, this invention relates to

40 (1) A pharmaceutical composition which comprises 2-[(2-pyridyl)methylsulfinyl]benzimidazole or a derivative thereof, which has an antiulcer activity, and a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium, and

(2) A method of producing a stabilized pharmaceutical composition which comprises incorporating a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium in a pharmaceutical composition
45 containing 2-[(2-pyridyl)methylsulfinyl]benzimidazole or a derivative thereof, which has an antiulcer activity.

The benzimidazole compounds having an antiulcer activity which are to be used in the practice of the invention are those compounds which are described in the above-cited laid-open patent specifications, for instance and are represented by the formula



10 wherein R¹ is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R² is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxy carbonylmethyl or alkylsulfonyl, R³ and R⁵ are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R⁴ is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4.

15 The compounds of the formula(I) can be produced by the methods described in the above-cited laid-open patent specifications or modifications thereof.

In the following, brief mention is made of the substituents in those compounds which have the formula - (I) and are already known.

20 Referring to R¹ in the above formula, C₁₋₆ alkyls may be mentioned as the alkyl represented by R¹; C₁₋₄ alkoxy as the alkoxy moiety of the carboalkoxy; C₁₋₄ alkoxy as the alkoxy moiety of the carboalkoxyalkyl and C₁₋₄ alkyls as the alkyl moiety; C₁₋₄ alkyls as the alkyl moiety of the carbamoylalkyl; C₁₋₄ alkoxy as the alkoxy; C₁₋₄ alkyls as the alkyl moiety of the hydroxalkyl; C₁₋₄ alkanoyls as the acyl; phenyl as the aryl; phenyl as the aryl moiety of the aryloxy; C₁₋₆ alkyls as the alkyl moiety of the alkylthio; and C₁₋₆ alkyls as the alkyl moiety of the alkylsulfinyl.

25 Referring to R², C₁₋₆ alkyls may be mentioned as the alkyl represented by R²; C₁₋₄ alkanoyls as the acyl; C₁₋₄ alkoxy as the alkoxy moiety of the carboalkoxy; C₁₋₄ alkyls as the alkyl moiety of the alkylcarbamoyl; C₁₋₄ alkyls as each of the alkyl moieties of the dialkylcarbamoyl; C₁₋₄ alkyls as the alkyl moiety of the alkylcarbonylmethyl; C₁₋₄ alkoxy as the alkoxy moiety of the alkoxy carbonylmethyl; and C₁₋₄ alkyls as the alkyl moiety of the alkylsulfonyl.

30 Referring to R³, R⁴ and R⁵, C₁₋₄ alkyls may be mentioned as the alkyl represented by any of them; C₁₋₄ alkoxy as the alkoxy; and C₁₋₄ alkoxy as each of the alkoxy moieties of the alkoxyalkoxy.

Referring to R⁴, C₁₋₆ alkoxy may be mentioned as the alkoxy, which may optionally be fluorinated.

35 Among those compounds of the above formula (I), (I) the compounds of which R¹ is hydrogen, methoxy or trifluoromethyl, R² is hydrogen, R³ and R⁵ are the same or different and each is hydrogen or methyl, R⁴ is fluorinated C₂₋₅ alkoxy and m is 1, (2) the compounds of which R¹ is hydrogen, fluorine, methoxy or trifluoromethyl, R² is hydrogen, R³ is hydrogen or methyl, R⁴ is C₃₋₈ alkoxy, R⁵ is hydrogen and m is 1, and (3) the compounds of which R¹ is hydrogen, fluorine, methoxy or trifluoromethyl, R² is hydrogen, R³ is C₁₋₄ alkoxy, R⁴ is C₁₋₆ alkoxy which may be fluorinated, R⁵ is hydrogen and m is 1.

Detailed mention is now made of the substituents in such novel compounds.

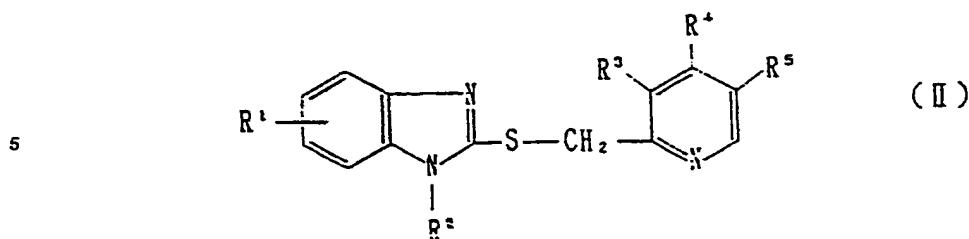
40 Referring to R³, the lower alkyl represented thereby is preferably C₁₋₄ lower alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, heptyloxy, heptyloxy or octyloxy and more preferably C₁₋₄ lower alkoxy.

45 Referring to R⁴, C₁₋₆ lower alkoxy may be mentioned as the lower alkoxy, which may optionally be fluorinated, and preferred examples are as mentioned above for R³. As the fluorinated lower alkoxy, there may be mentioned, for example, 2,2,2-trifluoroethoxy, 2,2,3,3,3-pentafluoropropoxy, 1-(trifluoromethyl)-2,2,2-trifluoroethoxy, 2,2,3,3-tetrafluoropropoxy, 2,2,3,3,4,4,4-heptafluorobutoxy and 2,2,3,3,4,4,5,5-octafluoropenoxy, and fluorinated C₂₋₄ lower alkoxy are preferred.

The position of R¹ is position 4 or position 5, preferably position 5.

50 Some methods of producing the above novel compounds [hereinafter referred to as "compounds of formula (I)"] are described below.

Said compounds can be produced by subjecting a compound of the formula



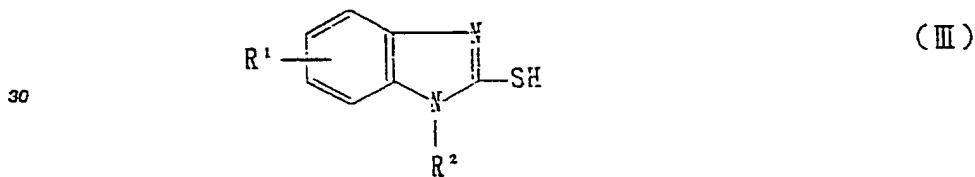
10 wherein R¹-R⁵ are as defined above, to oxidation.

10 The oxidizing agent to be used is, for example, meta-chloroperbenzoic acid, peracetic acid, trifluoroperacetic acid, permaleic acid or the like peracid, sodium bromite or sodium hypochlorite. Examples of the solvent to be used in carrying out the reaction are halogenated hydrocarbons such as chloroform and dichloromethane, ethers such as tetrahydrofuran and dioxane, amides such as dimethylformamide, and water. These solvents may be used either singly or in admixture. Said oxidizing agent is used preferably in an amount approximately equivalent or slightly excessive relative to the compound (II). Thus, said agent is used in an amount of about 1-3 equivalents, more preferably about 1 to 1.5 equivalents. The reaction is carried out at a temperature from about 0°C (ice cooling) to around the boiling point of the solvent used, generally at a temperature from about 0°C (ice cooling) to room temperature, preferably at a temperature of about 0°C to 10°C. The reaction time is generally about 0.1 to 24 hours, preferably about 0.1 to 4 hours.

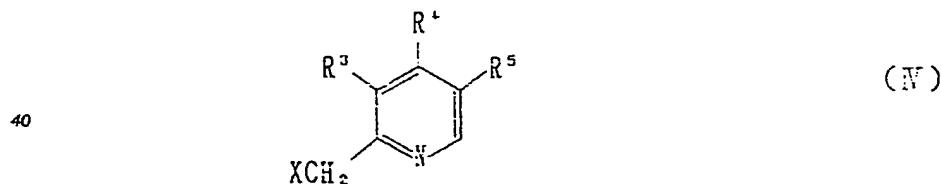
20 The desired novel compounds (I') produced by the above reaction can be isolated and purified by conventional means such as recrystallization, chromatography and so on.

20 Said compounds may be converted to pharmacologically acceptable salts by conventional means. As such salts, there may be mentioned hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate, sulfate, acetate and citrate, among others.

25 The novel compounds (II) can be produced by reacting a starting compound of the formula



35 wherein R¹ and R² are as defined above, with a starting compound of the formula



45 wherein R³-R⁵ are as defined above and X is a halogen atom.

45 The halogen atom represented by X is, for example, chlorine, bromine or iodine.

45 The reaction is carried out advantageously in the presence of a base. As said base, there may be mentioned alkali metal hydrides such as sodium hydride and potassium hydride, alkali metals such as metallic sodium, sodium alcoholates such as sodium methoxide and sodium ethoxide, alkali metal carbonates such as potassium carbonate and sodium carbonate, and organic amines such as triethylamine, among others. As the solvent to be used in carrying out the reaction, there may be mentioned, for example, alcohols such as methanol and ethanol, and dimethylformamide. The base is used generally in an amount slightly excessive relative to the equivalent amount but may also be used in a large excess. Thus, it is used in an amount of about 2-10 equivalents, preferably about 2-4 equivalents. The above reaction is carried out generally at a temperature of about 0°C to around the boiling point of the solvent used, preferably at about 50 20°C to 80°C, for a period of about 0.2-24 hours, preferably about 0.5-2 hours.

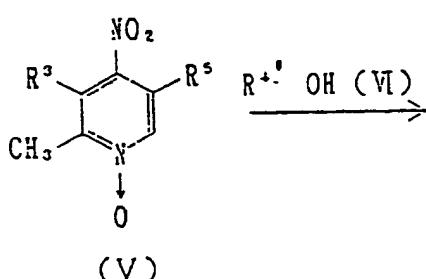
55 Some methods of producing the starting compounds (IV) are described below.

Among the compounds (IV), those compounds wherein R³ and R⁵ are the same or different and each is hydrogen or methyl and R⁴ is fluorinated C₂₋₅ alkoxy or C₃₋₈ alkoxy can be produced by the following process:

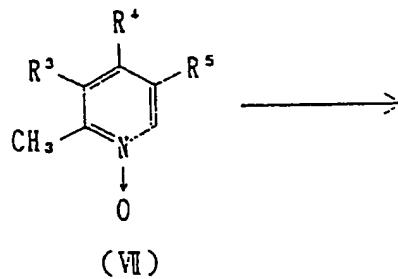
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Process 1)

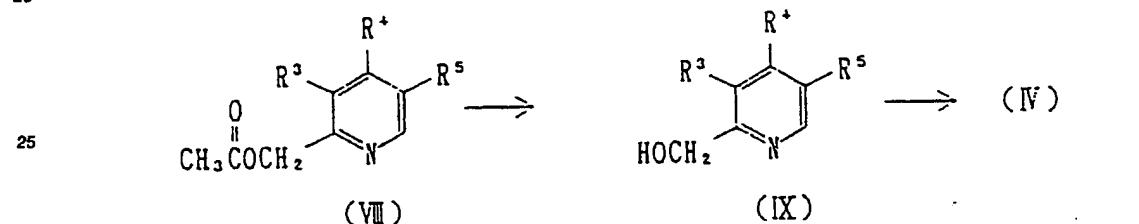
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A nitro compound of the formula (V), wherein R³ and R⁵ are as defined above, is reacted with an alcohol derivative of the formula R'⁴OH (VI) wherein R'⁴ is fluorinated C₂₋₅ alkyl or C₃₋₈ alkyl, in the presence of a base to give an alkoxy derivative of the formula (VII) wherein R³, R⁴ and R⁵ are as defined above. The base to be used in carrying out the reaction includes, among others, alkali metals such as lithium, sodium and potassium, alkali metal hydrides such as sodium hydride and potassium hydride, alcoholates such as

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potassium t-butoxide and sodium propoxide, alkali metal carbonates and hydrogen carbonates such as potassium carbonate, lithium carbonate, sodium carbonate, potassium hydrogen carbonate and sodium hydrogen carbonate, and alkali metal hydroxides such as

sodium hydroxide and potassium hydroxide. The alcohol derivative to be submitted to the reaction includes,

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among others, propanol, isopropanol, butanol, pentanol, hexanol, 2,2,2-trifluoroethanol, 2,2,3,3,3-pentafluoropropanol, 2,2,3,3-tetrafluoropropanol, 1-(trifluoromethyl)-2,2,2-trifluoroethanol, 2,2,3,3,4,4,4-heptafluorobutanol and 2,2,3,3,4,4,5,5-octafluoropentanol. While R'⁴OH itself may be used as a solvent in carrying out the reaction, ethers such as tetrahydrofuran and dioxane, ketones such as acetone and methyl ethyl ketone, acetonitrile, dimethylformamide and hexamethylphosphoric acid triamide, for instance, may also be used as solvents. An appropriate reaction temperature may be selected within the range of about 0°C (ice cooling) to around the boiling point of the solvent used. The reaction time is about 1-48 hours.

Heating (about 80-120°C) of the thus-obtained compound (VII) with acetic anhydride alone or in the presence of an inorganic acid such as sulfuric acid or perchloric acid gives an 2-acetoxyethylpyridine derivative of the formula (VIII) wherein R³, R⁴ and R⁵ are as defined above. The reaction period is generally about 0.1-10 hours.

The subsequent alkaline hydrolysis of the compound (VIII) gives a 2-hydroxymethylpyridine derivative of the formula (IX). Sodium hydroxide, potassium hydroxide, potassium carbonate and sodium carbonate, for instance, are usable as alkalis, and methanol, ethanol and water, among others, are usable as solvents. The reaction is generally conducted at about 20-60°C for about 0.1-2 hours.

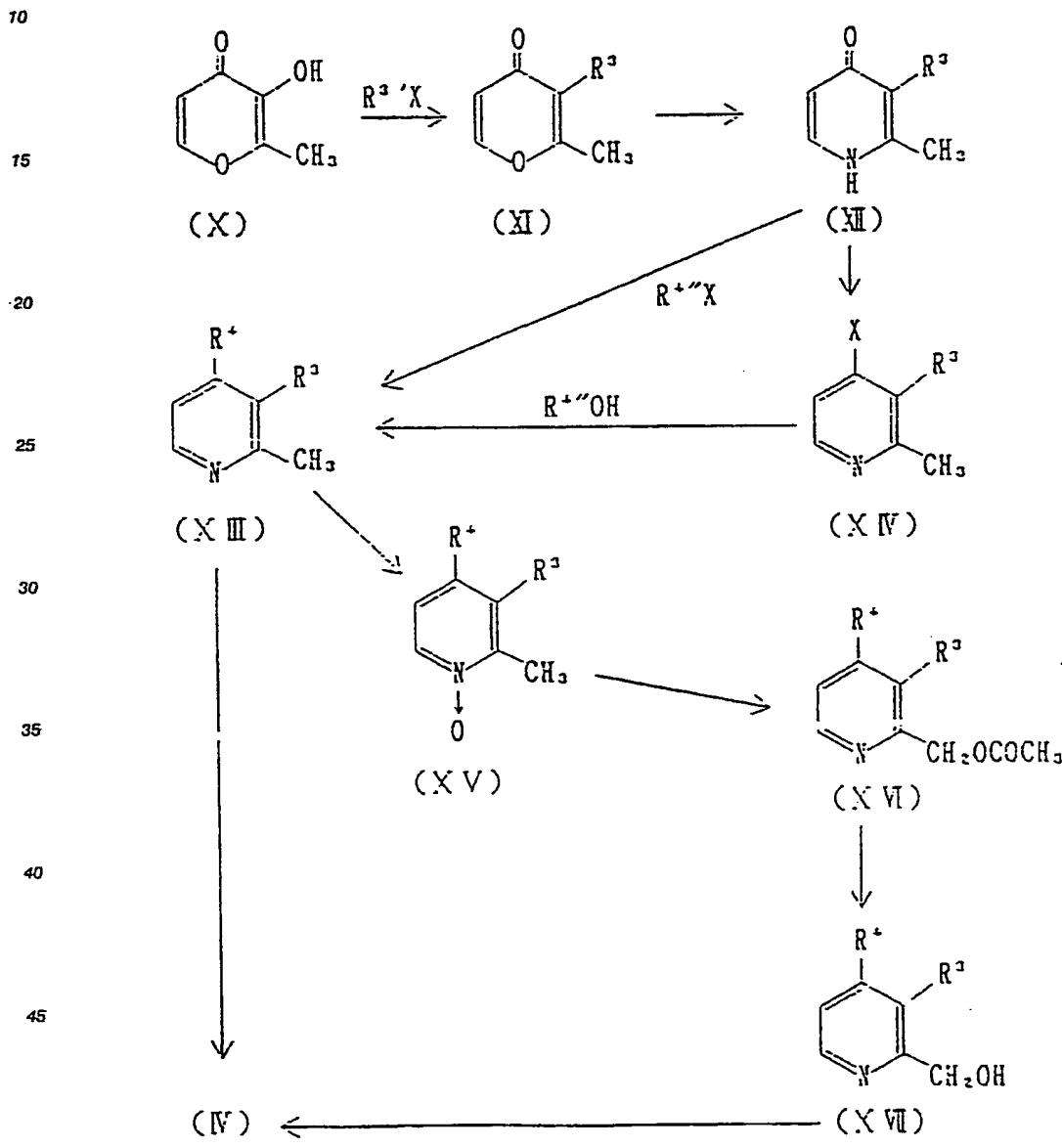
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The compound (IX) is further halogenated with a chlorinating agent such as thionyl chloride to give a 2-halomethylpyridine derivative of the formula (IV) wherein R³, R⁴ and R⁵ are as defined above and X is chlorine, bromine or iodine. Usable as solvents are, for example, chloroform, dichloromethane and tetrachloroethane. The reaction is generally carried out at about 20-80°C for about 0.1-2 hours.

The compound (IV) thus produced occurs in the form of a salt of hydrohalogenic acid corresponding to the halogenating agent used and it is generally preferable to subject said compound to reaction with the compound (III) immediately.

Among the compounds (IV), those compounds wherein R³ is C₁₋₄ lower alkoxy, R⁴ is alkoxy which may 5 optionally be fluorinated, and R⁵ is hydrogen can be produced by the following process:

Process 2)



Thus, maltol (X) is reacted with a alkyl halide of the formula R³X in the presence of silver oxide, for instance, to give a compound of the formula (XI). Reaction of (XI) with aqueous ammonia gives a pyridone derivative of the formula (XII). Direct alkylation of the compound (XII) with an alkyl halide, or halogenation of (XII) with a halogenating agent such as phosphorus oxychloride followed by reaction of the resultant halo derivative (XIV) with a lower alcohol of the formula R⁴ OH in the presence of a base gives a compound of the formula (XIII). The compound (XIII) can be converted to the compound (IV) by direct halogenation with 55

N-bromosuccinimide or chlorine, for instance. The compound (XIII) may also be converted to the compound (IV) by oxidizing the same with an oxidizing agent such as m-chloroperbenzoic acid, reacting the resulting compound (XV) with acetic anhydride, hydrolyzing the resulting compound (XVI) and halogenating the resulting compound (XVII) with a halogenating agent such as thionyl chloride.

5 The alkyl halide to be used in the production of the compound (XI) includes, among others, methyl iodide, ethyl iodide, propyl iodide, isopropyl iodide, butyl iodide, pentyl iodide and hexyl iodide, and the alkyl halide to be used in the production of the compound (XIII) further includes, in addition to those mentioned above for use in the production of the compounds (XI), 2,2,2-trifluoroethyl iodide, 2,2,3,3,3-pentafluoropropyl iodide, 2,2,3,3-tetrafluoropropyl iodide, 1-(trifluoromethyl)-2,2,2-trifluoroethyl iodide, 10 2,2,3,3,4,4,4-heptafluorobutyl iodide and 2,2,3,3,4,4,5,5-octafluoropentyl iodide, for instance. Such alkyl iodides are used in an amount of about 1-10 equivalents. Silver oxide, potassium carbonate, sodium carbonate or the like is used as a deacidifying agent and dimethylformamide, dimethylacetamide or the like is used as a solvent. The reaction is generally carried out at room temperature.

15 The halogenating agent to be used in the production of the compound (XIV) includes, among others, phosphorus oxychloride, phosphorus pentoxide and phosphorus tribromide and is used in an amount of 1 equivalent to a large excess. The reaction is carried out at a temperature of about 50-150°C. The alcohol to be used for the conversion of compound (XIV) to compound (XIII) includes methanol and ethanol and further those alcohol derivatives mentioned for use in process I) and is used in an amount of 1 equivalent to a large excess, and the base includes those sodium alcoholates and potassium alcoholates which correspond to the 20 respective alcohols as well as potassium t-butoxide, sodium hydride and so forth. An appropriate reaction temperature may be selected within the range of room temperature to the boiling point of the solvent used.

For direct bromination of the compound (XIII) with N-bromosuccinimide, the reaction is preferably carried out under light irradiation, and carbon tetrachloride, chloroform, tetrachloroethane or the like is used as a solvent.

25 The oxidizing agent to be used for the conversion of compound (XIII) to compound (XV) includes, among others, peracids such as meta-chloroperbenzoic acid, peracetic acid, trifluoroperacetic acid and permaleic acid as well as hydrogen peroxide. Usable as solvents for the reaction are halogenated hydrocarbons such as chloroform and dichloromethane, ethers such as tetrahydrofuran and dioxane, amides such as dimethylformamide, acetic acid and water, for instance, and these can be used either singly or in admixture. Said oxidizing agent is preferably used in an amount of about 1 equivalent to an excess relative to the compound (XIII), more preferably about 1-10 equivalents. The reaction is carried out at a temperature of about 0°C (ice cooling) to around the boiling point of the solvent used generally for a period of about 0.1-24 hours, preferably for about 0.1-4 hours.

35 The conversion of compound (XV) to compound (XVI) is effected by heating (at about 80-120°C) the compound (XV) with acetic anhydride alone or in the presence of an inorganic acid such as sulfuric acid or perchloric acid and so on. The reaction period is generally 0.1-10 hours.

40 The alkali to be used in the alkaline hydrolysis of compound (XVI) to compound (XVII) includes, among others, sodium hydroxide, potassium hydroxide, potassium carbonate and sodium carbonate. Methanol, ethanol and water, for instance, may be mentioned as usable solvents. The reaction is generally carried out at a temperature of about 20-60°C for a period of about 0.1-2 hours.

45 For the production of compound (IV) from compound (XVII), a chlorinating agent such as thionyl chloride or an organic sulfonic or organic phosphoric acid chloride such as methanesulfonyl chloride, p-toluenesulfonyl chloride or diphenylphosphoryl chloride is used. When a chlorinating agent such as thionyl chloride is used, it is used in an amount of 1 equivalent to a large excess relative to the compound (XVII) and a solvent such as chloroform, dichloromethane or tetrachloroethane is used, and the reaction is generally carried out at a temperature of about 20-80°C for a period of about 0.1-2 hours. When an organic sulfonic or organic phosphoric acid chloride is used, it is used in an amount of 1 equivalent to a slight excess relative to the compound (XVII) and the reaction is generally carried out in the presence of a base. As usable bases, there may be mentioned organic bases such as triethylamine and tributylamine and inorganic bases such as sodium carbonate, potassium carbonate and sodium hydrogen carbonate. The base is used in an amount of 1 equivalent to a slight excess. As usable solvents, there may be mentioned, for example, chloroform, dichloromethane, carbon tetrachloride and acetonitrile. An appropriate reaction temperature and an appropriate reaction can be selected within the ranges of about 0°C (ice cooling) to around the boiling point and several minutes to several hours, respectively.

55 The above-mentioned novel benzimidazole compounds have excellent gastric antisecretory activity, gastric mucosa-protecting activity and antiulcer activity but have low toxicity, so that they can be used in the treatment of digestive ulcers in mammals (e.g. mouse, rat, rabbit, dog, cat, human).

The basic inorganic salt of magnesium and that of calcium, which are to be used in accordance with the invention, are now described.

Said basic inorganic salt of magnesium includes, among others, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium alminate, synthetic hydrotalcite $[Mg_6Al_2(OH)_6\bullet CO_3\bullet 4H_2O]$ and aluminum magnesium hydroxide $[2.5MgO\bullet Al_2O_3\bullet xH_2O]$ and said basic inorganic salt of calcium includes, among others, precipitated calcium carbonate and calcium hydroxide. It is only required of such basic inorganic magnesium and calcium salts to show basicity (pH of not less than 7) when they are in the form of a 1% aqueous solution or suspension.

10 Said basic inorganic magnesium and calcium salts may be used either singly or in combination of two or more species in an amount which may vary depending on the kinds thereof but generally lies within the range of about 0.3-20 parts by weight, preferably about 0.6-7 parts by weight, per part by weight of the benzimidazole compounds.

15 The composition of the invention may further contain such additives as vehicles (e.g. lactose, corn starch, light silicic anhydride, microcrystalline cellulose, sucrose), binders (e.g. α -form starch, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone), disintegrating agents (e.g. carboxymethylcellulose calcium, starch, low substituted hydroxypropylcellulose), surfactants [e.g. Tween 80 (Kao-Atlas), Pluronic F68 (Asahi Denka; polyoxyethylene-polyoxypropylene copolymer)], antioxidants (e.g. L-cysteine, sodium sulfite, sodium ascorbate), lubricants (e.g. 20 magnesium stearate, talc), etc.

20 The composition of the invention is prepared by homogeneously admixing the above benzimidazole compound, the basic inorganic salt of magnesium and/or basic inorganic salt of calcium, and the above additives.

25 The particle sizes of said benzimidazole compound and said inorganic salt are not especially critical in a condition that they can be homogeneously admixed. For example, preferable particle size is about less than 100 μm , a more preferable one is about less than 20 μm .

The moisture amount in the composition is preferably about 6 -60%, more preferably about 20 -40% as equilibrium relative humidity (E.R.H.).

30 The method of admixing is optional if the benzimidazole compound can finally be in contact with the basic inorganic salt of magnesium and/or of calcium evenly. Thus, for example, the additives may be admixed with a mixture of the benzimidazole compound and the basic inorganic salt of magnesium and/or calcium as prepared by preliminary admixing, or the basic inorganic salt of magnesium and/or of calcium may be added to a mixture of the benzimidazole compound and the additives as prepared by preliminary admixing.

35 Said mixture can be made up into dosage forms suited for oral administration, such as tablets, capsules, powders, granules and fine granules, by per se known means.

Tablets, granules and fine granules may be coated by a per se known method for the purpose of masking of the taste or providing them with enteric or sustained release property. Usable as coating agents are, for example, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluornic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit (Röhm, West Germany; methacrylic acid-acrylic acid copolymer) and pigments such as titanium oxide and ferric oxide.

40 Tablets, granules, powders, fine granules and capsules can be produced by a conventional method - (e.g. the method described in the 10th edition of the Japanese Pharmacopeia under General Rules for Preparations). Thus, for example, tablets are produced by adding the basic inorganic salt of magnesium and/or of calcium to a mixture of the benzimidazole compound, vehicle and disintegrant, mixing, adding a binder, granulating the mixture, adding a lubricant etc. and tabletting the resultant granular composition. Granules are produced by extrusion in approximately the same manner as in the production of tablets or by coating nonpareils, which contain sucrose and corn starch, with a mixture of benzimidazole compound, a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium, and additives (e.g. sucrose, corn 50 starch, crystalline cellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone)

Capsules are produced by mere mixing and filling. The dosage forms thus obtained show excellent stability with slight changes in appearance and little decreases in content even after storage for a long period of time.

55 The pharmaceutical composition of the present invention as obtained in the above manner exhibits excellent gastric antisecretory, gastric mucosa-protecting and antiulcer activities and has low toxicity and therefore can be used in the treatment of digestive ulcers in mammals (e.g. mouse, rat, rabbit, dog, cat, pig, human).

The pharmaceutical composition of the invention can be orally administered for the treatment of digestive ulcers in mammals in admixture with pharmacologically acceptable carriers, vehicles, diluents and so forth and in the form of capsules, tablets, granules and some other dosage forms, as mentioned hereinabove. The dose as the benzimidazole compound lies within the range of about 0.01 mg to 30 mg/kg/day, preferably about 0.1 mg to 3 mg/kg/day.

The following reference examples and working examples as well as the experimental examples described later herein illustrate the present invention in more detail but are by no means limitative of the present invention.

10

Reference Example 1

A mixture of 2,3-dimethyl-4-nitropyridine-1-oxide (2.0 g), methyl ethyl ketone (30 ml), 2,2,3,3,3-pentafluoropropanol (3.05 ml), anhydrous potassium carbonate (3.29 g) and hexamethylphosphoric acid triamide (2.07 g) was heated at 70-80°C with stirring for 4.5 days. Then, the insoluble matter was filtered off and the filtrate was concentrated. Water was added to the residue and the mixture was extracted with ethyl acetate. The extract layer was dried over magnesium sulfate, then the solvent was distilled off, and the residue was applied to a silica gel column (50 g). Elution with chloroform-methanol (10:1) and recrystallization from ethyl acetate-hexane gave 2.4 g of 2,3-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide as colorless needles. Melting point 148-149°C.

The following compounds (VII) were produced from the corresponding compounds (V) in the same manner as above.

Compounds (VII)

25

	R ³	R ⁵	R ⁴	Melting point (°C)
30	CH ₃	H	OCH ₂ CF ₃	131.0-131.5
Note 1)	H	H	OCH ₂ CH ₂ CH ₃	Oil
Note 2)	CH ₃	H	OCH ₂ CH ₂ CH ₃	Oil

35

Note 1): NMR spectrum (CDCl₃) δ: 1.01 (3H, t, J = 7 Hz), 1.81 (2H, m), 2.50 (3H, s), 3.93 (2H, t, J = 7 Hz), 6.50-6.80 (2H, m), 8.10 (1H, d, J = 7 Hz)

Note 2): NMR spectrum (CDCl₃) δ: 1.07 (3H, t J = 7.5 Hz), 1.65-2.02 (2H, m), 2.21 (3H, s), 2.52 (3H, s), 3.99 (2H, t, J = 6 Hz), 6.68 (1H, d, J = 6 Hz), 8.15 (1H, d, J = 6 Hz)

40

Reference Example 2

Concentrated sulfuric acid (2 drops) was added to a solution of 2,3-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide (2.5 g) in acetic anhydride (8 ml) and the mixture was stirred at 110°C for 2 hours and then concentrated. The residue was dissolved in methanol (30 ml), 2 N aqueous sodium hydroxide (20 ml) was added, and the mixture was stirred at room temperature for 2 hours. After concentration, water was added to the residue and the mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate, the solvent was then distilled off, and the residue was applied to a silica gel (50 g) column. Elution with chloroform-methanol (10:1) and recrystallization from isopropyl ether gave 1.6 g of 2-hydroxymethyl-3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine as a brown oil.

NMR spectrum (CDCl₃) δ: 2.07 (3H, s), 4.28 (1H, brs), 4.49 (2H, t, J = 12 Hz), 4.67 (2H, s), 6.69 (1H, d, J = 5 Hz), 8.34 (1H, d, J = 5 Hz)

The following compounds (IX) were produced from the corresponding compounds (VII) in the same manner as mentioned above.

Compounds (IX)

	R ³	R ⁵	R ⁴	Melting point (°C)
5	CH ₃	H	OCH ₂ CF ₃	93.5-94.0
10	Note 1) H	H	OCH ₂ CH ₂ CH ₃	Oil
	Note 2) CH ₃	H	OCH ₂ CH ₂ CH ₃	Oil

15 Note 1) NMR spectrum (CDCl₃) δ: 1.0 (3H, t, J = 7.5 Hz), 1.79 (2H, m), 3.92 (2H, t, J = 6 Hz), 4.51-4.90 (1H, br), 4.68 (2H, s), 6.68 (1H, dd, J = 2 and 6 Hz), 6.80 (1H, d, J = 2 Hz), 8.28 (1H, d, J = 6 Hz)
Note 2) NMR spectrum (CDCl₃) δ: 1.03 (3H, t, J = 7.5 Hz), 1.82 (2H, m), 2.02 (3H, s), 3.95 (2H, t, J = 6 Hz), 4.62 (2H, s), 5.20 (1H, brd, s), 6.68 (1H, d, J = 6 Hz), 8.25 (1H, d, J = 6 Hz)

20 Reference Example 3

Thionyl chloride (0.2 ml) was added to a solution of 2-hydroxymethyl-3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine (350 mg) in chloroform (10 ml) and the mixture was refluxed for 30 minutes and then concentrated. The residue was dissolved in methanol (5 ml) and the solution was added to a mixture of 2-mercaptopbenzimidazole (200 mg), 28% sodium methoxide solution (1 ml) and methanol (6 ml). The resultant mixture was refluxed for 30 minutes. The methanol was distilled off, water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with dilute sodium hydroxide solution and dried over magnesium sulfate. The solvent was then distilled off, and the residue was applied to a silica gel (20 g) column. Elution with ethyl acetate-hexane (2:1) and recrystallization from ethyl acetate-hexane gave 370 mg of 2-[[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-2-pyridyl] methylthio]benzimidazole hemihydrate as colorless plates. Melting point 145-146°C.

The following compounds (II) were produced by reacting the compound (III) with the corresponding compound (IV) in the same manner as mentioned above.

35 Compounds (II)

	R ¹	R ²	R ³	R ⁵	R ⁴	Melting point (°C)
40	H	H	CH ₃	H	OCH ₂ CF ₃	149-150
	H	H	H	H	OCH ₂ CH ₂ CH ₃	84-86
45	Note)	H	H	CH ₃	H	OCH ₂ CH ₂ CH ₃

50 Note) NMR spectrum (CDCl₃) δ: 0.98 (3H, t, J = 7.5 Hz), 1.54-1.92 (2H, m), 2.15 (3H, s), 3.80 (2H, t, J = 6 Hz), 4.43 (2H, s), 6.55 (1H, d, J = 6 Hz), 7.09 (2H, m), 7.50 (2H, m), 8.21 (1H, d, J = 6 Hz)

50 Reference Example 4

A solution of m-chloroperbenzoic acid (1.3 g) in chloroform (15 ml) was added dropwise to a solution of 2-[[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-2-pyridyl]methylthio]benzimidazole(2.2 g) in chloroform (20 ml) with ice cooling over 30 minutes and, then, the reaction mixture was washed with saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulfate and concentrated. The concentrate was

applied to a silica gel (50 g) column. Elution with ethyl acetate and recrystallization from acetone-isopropyl ether gave 1.78 g of 2-[[3-methyl-4-(2,2,3,3-pentafluoropropoxy)-2-pyridyl]methylsulfinyl]benzimidazole [hereinafter sometimes referred to as compound (A)] as pale yellow prisms. Melting point 161-163°C - (decomposition).

5 The following compounds (I) [hereinafter sometimes referred to as compound (B), compound (C) and compound (D), respectively] were produced in the same manner from the corresponding compounds (II).

Compounds (I)

	R ¹	R ²	R ³	R ⁵	R ⁴	Melting point (°C)	
	(B)	H	H	CH ₃	H	OCH ₂ CF ₃	178-182 (decomp.)
15	(C)	H	H	H	H	OCH ₂ CH ₂ CH ₃	123-125 (decomp.)
	(D)	H	H	CH ₃	H	OCH ₂ CH ₂ CH ₃	81-83

20

Example 1

25 Of the components given below, the compound (A), magnesium hydroxide, L-cysteine, corn starch and lactose were mixed together, then microcrystalline cellulose, light silicic anhydride and magnesium stearate, each in half the intended amount, were added. After sufficient admixing, the mixture was compression-molded on a dry granulator (roller compactor; Freund, Japan). The compressed mass was ground in a mortar, the resultant granular mass was passed through a round sieve (16 mesh). The remaining portions of microcrystalline cellulose, light silicic anhydride and magnesium stearate were added to the sieved mass and, after admixing, the whole mixture was made up into tablets each weighing 250 mg on a rotary tabletting machine (Kikusui Seisakusho, Japan). Composition per tablet:

	Compound (A)	50 mg
35	Magnesium hydroxide	.30 mg
	L-Cysteine	20 mg
40	Corn starch	20 mg
	Lactose	65.2 mg
45	Microcrystalline cellulose	60 mg
	Light silicic anhydride	1.8 mg
	Magnesium stearate	3.0 mg
50	Total	250.0 mg

Example 2

55 Tablets were produced in the same manner as in Example 1 except that omeprazole (Note) was used instead of the compound (A).

Note: 5-Methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole

Example 3

5 Of the components given below, the compound (B), precipitated calcium carbonate, corn starch, lactose and hydroxypropylcellulose were mixed together, water was added, and the mixture was kneaded, then dried in a vacuum at 40°C for 16 hours, ground in a mortar and passed through a 16-mesh sieve to give granules. To this was added magnesium stearate and the resultant mixture was made up into tablets each
 10 weighing 200 mg on a rotary tabletting machine (Kikusui Seisakusho, Japan). Composition per tablet:

	Compound (B)	30 mg
15	Precipitated calcium carbonate	50 mg
	Corn starch	40 mg
20	Lactose	73.4 mg
	Hydroxypropylcellulose	6 mg
	Magnesium stearate	0.6 mg
25	Water	(0.05 ml)
	Total	200.0 mg

30 **Example 4**

Tablets were produced in the same manner as in Example 3 except that timoprazole (Note) was used instead of the compound (B).

35 Note: 2-[(2-Pyridyl)methylsulfinyl]benzimidazole

Example 5

40 The ingredients given below were mixed well in the proportions given below, water was added, and the mixture was kneaded and granulated in an extruder granulator (Kikusui Seisakusho; screen size 1.0 mm Ø). The granules were immediately converted to spherical form in a spheronizer (Fuji Powder's Marumerizer, Japan; 1,000 rpm). The spherical granules were then dried under vacuum at 40°C for 16 hours and passed through round sieves to give 12-to 42-mesh granules. Composition per 200 mg of granules

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50	Compound (B)	30 mg
	Heavy magnesium carbonate	20 mg

55

	Corn starch	80 mg
5	Microcrystalline cellulose	20 mg
	Carboxymethylcellulose calcium	10 mg
	Hydroxypropylcellulose	10 mg
10	Pluronic F68	4 mg
	Lactose	26 mg
15	Water	(0.1 ml)
	Total	200 mg

20 Example 6

Granules were produced in the same manner as in Example 5 except that the compound (D) was used instead of the compound (B).

25 Example 7

Enteric granules were produced by coating the granules obtained in Example 3 with an enteric coating composition specified below using a fluidized bed granulator (Okawara, Japan) under conditions such that the inlet air temperature was 50°C and the granule temperature was 40°C. No. 1 hard capsules were filled 30 with the enteric granules thus obtained in an amount of 260 mg per capsule using a capsule filling machine (Parke-Davis, U.S.A.). Enteric coating composition:

Eudragit L-30D 138 mg (solids 41.4 mg)

Talc 4.1 mg

Polyethylene glycol 6000 12.4 mg

35 Tween 80 2.1 mg

Water 276μl

Composition of enteric granules:

40	Granules of Example 5	200 mg
	Enteric coat	60 mg
45	Total	260 mg

Composition per capsule:

50	Enteric granules	260 mg
	No. 1 hard capsule	76 mg
55	Total	336 mg

Example 8

Of the components given below, the compound (B), magnesium carbonate, sucrose, corn starch and crystalline cellulose were thoroughly mixed together to obtain dusting powder.

5 Nonpareils were put on a centrifugal fluidized coatinggranulator (CF-360 Freund, Japan) and then coated with the dusting powder as described above, while spraying hydroxypropylcellulose solution [4% - (w/w)], to give spherical granules. The spherical granules were dried in a vacuum at 40°C for 16 hours and then passed through round sieves to give 12 to 32-mesh granules. Composition per 190 mg of granules:

10

	Nonpareil	75 mg
15	Compound (B)	15 mg
	Magnesium carbonate	15 mg
	Sucrose	29 mg
20	Corn starch	27 mg
	Crystalline cellulose	27 mg
25	Hydroxypropylcellulose [Hydroxypropoxy group content: 53.4-77.5%]	2 mg
	Water	(0.05 ml)
30	Total	190 mg

Example 9

35

Enteric granules were produced by coating the granules obtained in Example 8 with an enteric coating composition, specified below using a fluidized bed granulator (Okawara, Japan) under conditions such that inlet air temperature was 50°C and the granule temperature was 40°C. No. 2 hard capsules were filled with the enteric granules thus obtained in an amount of 240mg per capsule using a capsule filling machine -

40 (Parke-Davis, USA). Enteric coating composition:

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	Eudragit L-30D	104.7 mg (solids 31.4 mg)
5	Talc	9.6 mg
	Polyethylene glycol 6000	3.2 mg
10	Tween 80	1.6 mg
	Titanium oxide	4.2 mg
	Water	(220 µl)

15 Composition of enteric granules:

	Granules of Example 8	190 mg
	Enteric coat	50 mg
20	Total	240 mg
	Composition per capsule:	
25	Enteric granules	240 mg
	No. 2 hard capsule	65 mg
	Total	305 mg

30 Experimental Example I

Granules were produced by the method of Example 5 and, after storage at 50°C and 75% RH for 1 week, were observed for changes in appearance. Granules were also produced in the same manner except that lactose was used instead of heavy magnesium carbonate or that one of other additives specified below in Table I.

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Table 1

5	Additive	Changes in appearance after 1 week at 50°C and 75% RH
10	The invention:	
	Heavy magnesium carbonate	-
15	Magnesium oxide	-
	Magnesium metasilicate aluminate	-
20	Synthetic hydrotalcite	-
	Aluminum magnesium hydroxide	-
25	Magnesium silicate	-
	Precipitated calcium carbonate	-
	Magnesium hydroxide	-
30	Controls:	
	Sodium carbonate	+ (to yellow)
	Potassium carbonate	+ (to yellow)
35	Sodium hydrogen carbonate	+ (to yellow)
	Magnesium chloride	++ (to violet)
40	Magnesium sulfate	++ (to violet)
	Calcium chloride	++ (to violet)
	Aluminum silicate	+ (to violet)
45	No additive (lactose)	++ (to violet)

Notes: - : No changes in

50 + : Moderately

++ : Severely

As a result, no substantial changes in appearance were noted for the compositions supplemented with
55 the additives of the invention.

Experimental Example 2

5 Granules were produced in the same manner as in Example 5 except that the compound (A), the compound (C), the compound (D), omeprazole or timoprazole was used instead of the compound (B). After storage at 50°C and 75% RH for 1 week, they were observed for changes in appearance. As a control to each composition, granules were also produced in the same manner except that lactose was used instead of heavy magnesium carbonate and stored under the same conditions.

	Compound	Additive	Changes in appearance after 1 week at 50°C and 75% RH
10	Compound (A)	Invention: Heavy magnesium carbonate	-
15		Control: Lactose	++
20	Omeprazole	Invention: Heavy magnesium carbonate	-
		Control: Lactose	++
25	Timoprazole	Invention: Heavy magnesium carbonate	-
		Control: Lactose	++
30	Compound (C)	Invention: Heavy magnesium carbonate	-
		Control: Lactose	++
35	Compound (D)	Invention: Heavy magnesium carbonate	-
40		Control: Lactose	++

Notes: - : No changes

45 ++ : Severely

As is evident from the above results, the pharmaceutical compositions of the invention were all stable whether the active ingredient was the compound (A), omeprazole, timoprazole, the compound (C) or the compound (D).

50

Experimental Example 3

Pharmaceutical compositions were produced in the same manner as in Examples 3 and 5 except that different basic inorganic Mg or Ca salts were used or that lactose was used as a control, and Example 7. After storage at 50°C and 75% RH for 1 week or at 40°C for 6 months, the compositions were observed for changes in appearance and for active ingredient content (residual percentage).

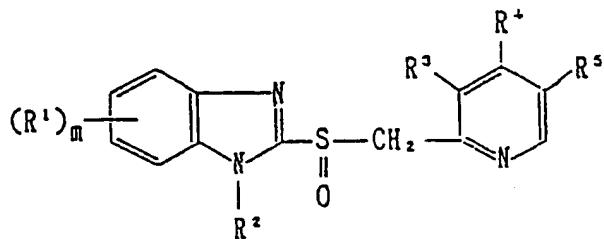
Table 2

Additive	Initial		50°C, 75% RH, 1 week		40°C, 6 months		
	Appearance	Content	Appearance	Content	Appearance	Content	
<u>Tablets made by the procedure of Example 3</u>							
Invention	Heavy magnesium carbonate	Appearance Content	White 100%	No change 98.0%	No change 99.5%	No change 99.5%	
Precipitated calcium carbonate	Appearance Content	White 100%	No change 97.4%	No change 96.5%	No change 96.5%	No change 96.5%	
Magnesium silicate	Appearance Content	White 100%	No change 94.5%	No change 95.0%	No change 95.0%	No change 95.0%	
Control	No addition (lactose)	Appearance Content	Pale violet 100%	Dark violet 73.5%	Dark violet 82.1%	Dark violet 82.1%	
<u>Granules made by the procedure of Example 5</u>							
Invention	Heavy magnesium carbonate	Appearance Content	White 100%	No change 98.2%	No change 99.1%	No change 99.1%	
Precipitate calcium carbonate	Appearance Content	White 100%	No change 97.2%	No change 98.6%	No change 98.6%	No change 98.6%	
Magnesium oxide	Appearance Content	White 100%	No change 99.4%	No change 99.0%	No change 99.0%	No change 99.0%	
Control	No addition (lactose)	Appearance Content	Pale violet 100%	Dark violet 84.2%	Dark violet 89.4%	Dark violet 89.4%	Dark violet 89.4%
<u>Capsules of Example 7</u>							
Invention	Heavy magnesium carbonate	Appearance Content	White 100%	No change 98.4%	No change 99.1%	No change 99.1%	No change 99.1%

The above results clearly indicate that the compositions of the invention show no changes in appearance at all and are stable in terms of the active ingredient content.

Claims

I. A pharmaceutical composition which comprises a compound of the formula



15 wherein R¹ is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R² is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxy carbonylmethyl or alkylsulfonyl, R³ and R⁵ are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R⁴ is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4, and a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium.

20 2. A pharmaceutical composition as claimed in claim I, wherein the compound is 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole.

3. A pharmaceutical composition as claimed in claim I, wherein the compound is 2-[[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-2-pyridyl]methylsulfinyl]benzimidazole.

25 4. A pharmaceutical composition as claimed in claim I, wherein the compound is 2-[(4-propoxy-2-pyridyl)methylsulfinyl]benzimidazole.

5. A pharmaceutical composition as claimed in claim I, wherein the compound is 2-[(3-methyl-4-propoxy-2-pyridyl)methylsulfinyl]benzimidazole.

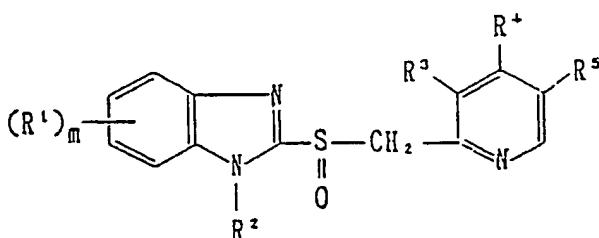
30 6. A pharmaceutical composition as claimed in claim I, wherein the compound is 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole.

7. A pharmaceutical composition as claimed in claim I, wherein the basic inorganic salt of magnesium is magnesium carbonate.

35 8. A pharmaceutical composition as claimed in claim I, wherein the basic inorganic salt of calcium is precipitated calcium carbonate.

9. A pharmaceutical composition as claimed in claim I, wherein the composition is in particles and enteric-coated.

40 10. A method of producing a stabilized pharmaceutical composition which comprises incorporating a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium in a pharmaceutical composition containing a compound of the formula



50 wherein R¹ is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R² is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxy carbonylmethyl or alkylsulfonyl, R³ and R⁵ are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R⁴ is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4.

55 II. The use of a pharmaceutical composition for the manufacture of an antiulcer agent.

ELKINGTON AND FIFE

Chartered Patent Agents & European Patent Attorneys
Patents Trade Marks Designs

SYDNEY SMITH, M.A., C.P.A., E.P.A.
J. J. LAREDO, M.Sc., C.P.A., E.P.A.
J. I. MARCHANT, B.Sc., C.P.A., E.P.A.
G. A. BOON, M.A., C.P.A., E.P.A., M.I.T.M.A.
DIANA KYLE, B.Sc., C.P.A., E.P.A.
J. H. LEWIN, M.A., C.P.A., E.P.A., M.I.T.M.A.
CLIVE FROUD, B.Sc., C.P.A., E.P.A.
FIONA CRAWFORD, M.A., C.P.A., E.P.A.

P. J. CHARLTON, B.Sc., C.P.A., E.P.A.

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TELEPHONE 01-405 3505/6 01-405 3030
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FAX (GROUPS 2 & 3) 01-405 1508
SEVENOAKS OFFICE & ACCOUNTS
52/55 HIGH STREET
SEVENOAKS, KENT TN13 1JF
TEL. SEVENOAKS (0732) 458881/459681
AND AT MUNICH

CONSULTANT
D. R. FENTIMAN, C.P.A.

2nd July, 1987.

EUROPEAN PATENT OFFICE,
Branch at The Hague,
Receiving Section,
P.B. 5818 Patentlaan 2,
2280 HV RIJSWIJK (ZH),
THE NETHERLANDS.

REGISTERED MAIL.

Dear Sirs,

Re: European Patent Appln. No. 87 301244.7
TAKEDA CHEMICAL INDUSTRIES, LTD.

We thank you for your letter of 9th June, 1987, with the suggested title. This is in principle acceptable, but we think, with respect, that the title should be extended to refer to the use of the pharmaceutical compositions of the invention as antiulcer agents. Accordingly, we suggest the following title:

"Stabilized pharmaceutical composition comprising a benzimidazole compound, its production and its use as an antiulcer agent".

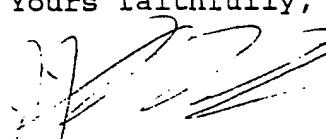
In reviewing the application in connection with the title, we noticed a clerical error in Claim 11 which clearly was intended to refer to preceding claims since it is not meaningful as it stands.

We, accordingly, ask that Claim 11 should be amended by the insertion after the words "...a pharmaceutical composition" of the words "according to any of Claims 1-9". A photostat of page 40 on which the desired amendment is indicated in manuscript is attached. We also file herewith in triplicate a new page 40 incorporating this amendment only.

In our respectful submission, the need for such amendment and its basis in the application are self-evident. We, accordingly, respectfully ask for the necessary action to be taken.

Yours faithfully,

Encs.


J. J. LAREDO
European Patent Attorney
Elkington and Fife